xenogeneic light chain immunoglobulin locus is human.

REMARKS

Applicants have amended claims 86-88 and 104-106 to more clearly point out what applicants regard as their invention. Specifically, applicants make explicit that the human V segment genes referred to in the claims are human V segment genes found on human chromosome 14. Upon entry of the amendments, claims 83-88, 95-97 and 104-109 will be pending in this application. None of the amendments adds new matter.

Applicants request entry of the amendments and reconsideration of the claims.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 83-88, 95-97 and 104-109 stand rejected under 35 U.S.C. § 112, first paragraph (enablement). Specifically, the Examiner asserts that human VH genes are also found on chromosomes 15 and 16 and that the specification discloses only "a single YAC vector which comprises a Spe restriction fragment of the germline human heavy chain Ig locus which includes V6, the D segment genes, the J segment genes, Cμ and Cδ". In the Examiner's view, the specification lacks guidance for obtaining, and thus it would require undue experimentation to obtain, a DNA sequence that includes other VH genes from chromosome 14 or VH genes from chromosomes 15 and 16.

Claims 86-88, 95-97 an 104-109 stand rejected under 35 U.S.C. § 112, first paragraph, also as lacking written description in the specification. Specifically, the Examiner states that the "specification lacks written description for functional V segment genes distal to the D segment genes on chromosome 14 and for V segment genes present on chromosomes 15 and 16."

Applicants believe that claims 83-85 were mistakenly included in the enablement rejection. Those claims are directed to transgenic mice in which both copies of the endogenous immunoglobulin heavy chain locus and one or both copies of the endogenous immunoglobulin light chain locus are inactivated. None of those claims refers to human DNA. Accordingly, applicants' will discuss the enablement and written description rejections with regard to claims 86-88, 95-97 and 104-109 only. As to those rejections, applicants traverse.

Applicants have amended claims 86-88 and claims 104-106 to clarify that the human immunoglobulin heavy chain V segment genes are VH genes found on human chromosome 14. The application, as filed, discloses at least three YACs each of which contains multiple human chromosome 14 VH genes and a transgenic mouse with multiple human VH genes from chromosome 14.

For example, at page 56, lines 7-23, describes the cloning of two YACs (205 kb and 215 kb) each of which contained "at least 5 VH genes including two VH1, one VH2, one VH4 and one VH6 gene." Page 57, lines 1-17, describes the cloning of a third YAC (230 kb). Page 59, lines 15- to page 60, line 3, describes Southern analysis of the 230 kb YAC with VH probes confirming the presence in the YAC of human VH1, VH2, VH4 and VH6 genes and of human DNA from the "5'end of the most 3' VH2 gene and extending to an EcoRI site 3' of the delta locus" (citation omitted). Finally, page 69, line 29 to page 70, line 34, describes the production of transgenic mice from ES cells containing the human DNA from the 230 kb YAC.

In view of this disclosure, the application, as filed, enables and provides written description for the full scope of claims 86-88, 95-97 and 104-109. Accordingly,

applicants request that the rejections under § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. §§ 102(e) and 103

Claims 83 and 85 stand rejected under 35 U.S.C. § 102(e) as "anticipated" by United States Patent 5,591,669 (Krimpenfort et al.) ("Krimpenfort"). Specifically, in the previous Office Action (Paper No. 41) the Examiner stated that "Krimpenfort discloses gene targeting of the J region of endogenous heavy chain immunoglobulin alleles in ES cells and further discloses that the embryonic stem (ES) cells having the inactivated J region endogenous alleles produce mice incapable of producing endogenous (murine) immunoglobulins."

Claims 84, 86-88 and 95-97 stand rejected under 35 U.S.C. § 103 as "unpatentable" over Krimpenfort. In the previous Office Action, the Examiner stated that although Krimpenfort does not disclose inactivation of an immunoglobulin light chain, "it would have been obvious" to apply the same method used on the heavy chain to inactivate the mouse light chain.

The Examiner acknowledged applicants' argument that the inactivated mouse endogenous immunoglobulin loci as recited in claims 83-85 (and the claims that depend from them) had already been found patentable over Krimpenfort by the Examiner in connection with claims issued in United States patent 5,939,598. The Examiner stated, however, that applicants are required to make the arguments of record in this application.

Claim 83, the only independent claim, and the claims that depend from it, are directed to a transgenic mouse comprising in its germline inactivated endogenous

immunoglobulin heavy chain loci in which all of the J segment genes from both copies of the locus are deleted to prevent rearrangement and to prevent formation of a transcript of a rearranged locus and the expression of an endogenous immunoglobulin heavy chain from the inactivated loci.

Claim 84 is directed to a transgenic mouse according to claim 83, further comprising at least one inactivated endogenous immunoglobulin light chain locus in which all of the J segment genes are deleted to prevent rearrangement and to prevent formation of a transcript of a rearranged locus and the expression of an endogenous immunoglobulin light chain from the inactivated loci.

Krimpenfort does not teach or suggest such transgenic mice. Instead, Krimpenfort primarily relates to the production of transgenic animals which are depleted in T cells or B cells. Krimpenfort refers to methods for producing such lymphocyte depleted animals using a transgene consisting of a functionally rearranged gene encoding a "lymphatic polypeptide" or "lymphatic polypeptide variant" (see col. 7, lines 25-28; col. 9, lines 32-35). The polypeptide or variant encoded by the transgene is expressed in a cell and suppresses expression of the endogenous allele through dominant negative suppression, also referred to as allelic exclusion.

Krimpenfort makes brief reference to a method for preventing expression of an endogenous immunoglobulin locus by inserting a stop codon into the locus. It is common general knowledge that a stop codon works at the level of translation. Thus, the system referred to in Krimpenfort is meant to disrupt translation of a rearranged immunoglobulin gene. That is not applicants' invention. As reflected in claims 83-88 and 95-97, according to applicants' invention, the endogenous locus is modified so as to prevent rearrangement of the locus

and to prevent formation of a transcript of a rearranged locus. Applicants submit herewith a Figure with a schematic representation of the difference between the method and mice referred to in Krimpenfort and the method and mice of applicants' invention. Because the method for inactivating the endogenous heavy chain locus in Krimpenfort is different from the method used by applicants, the transgenic mice produced by the Krimpenfort method are different from the transgenic mice of the invention.

Krimpenfort, thus, does not disclose or even suggest the transgenic mouse of claim 83. For the same reasons, Krimpenfort also neither teaches nor suggests a transgenic mouse according to claim 84. Accordingly, the transgenic mice of claims 83 and 84, and of the claims that depend from them, are novel and non-obvious over the Krimpenfort.

In view of the above, applicants request withdrawal of the rejections and reconsideration and allowance of the amended claims.

Respectfully submitted,

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Commissioner for Patents Washington, D.C. 20231, on April 4, 2001
JANE T. GUNNISON
Name of person signing
Jane T. Gunnison
Signature of person signing

Jane T. Gunnison

Jane T. Gunnison (Reg. No. 38,479)
Attorney for Applicants
c/o FISH & NEAVE
1251 Avenue of the Americas
New York, New York 10020-1104
Tel.: (212) 596-9000